REMARKS

I. Status of the Claims. Claims 1-22, 25, 26, 228, 35, 37-39, 64, and 66-85 are pending. Claims 22 and 37 have been amended to use language that more clearly defines the claimed invention. The respective scopes of claims 22 and 37 are unchanged. Accordingly, by this Amendment, no new matter has been added to the application.

II. Request for Priority Statement. The Examiner has requested that the common assignee of the instant application and the co-pending '553 application state which entity is the prior inventor of the alleged conflicting subject matter in claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 of the instant application and claims 36-96 of the '553 application.

In first response, in order for the instant response to be complete, the common assignee of the '553 application and the instant application indicates that, to the extent there is conflicting subject matter in claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 of the instant application and claims 36-96 of the '553 application (which Applicant does not believe to be the case), the subject matter claimed in the '553 application is the prior invention.

In second response, it is noted that the Examiner's request is believed to be unnecessary. All rejections under section 102(e) that are based on the '553 application or under 102(b) based on the counterpart international publication WO 99/47680 ("the '680 publication") have been withdrawn. The Examiner thus acknowledges that the '553 application and the '680 publication do not anticipate the instant claims. The subject matter of the claims of the '553 application is fully disclosed in the specification of the '553 application. Thus, because the specification of the '553 application does not anticipate the instantly pending claims, neither can the claims of the '553 application anticipate the instantly pending claims. Accordingly, to the extent, arguendo, that the claims of the '553 patent could be applied against the instant claims under sections 102(f) or 102(g), it would be to apply these sections in an obvious rejection under section 103(a). Such an obviousness rejection would, however, be improper. According to section 103(c)(1):

> Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under [section 103] where the subject matter and the claimed invention were, at the time the claimed invention was made, owned or subject to an obligation of assignment to the same person.

Applicant confirms that all inventors of the subject matter disclosed and claimed in the '553 patent and all inventors of the subject matter disclosed and presently claimed in the instant application were at all times subject to an obligation of assignment to ALK Abello A/S. Accordingly, the subject matter of the '553 patent may not be used in an obviousness rejection of the instant claims.

Because the instant claims are not anticipated by the claims of the '553 application and the subject matter of the '553 application that qualifies under sections 102(e), (f), or (g) may not be used in an obviousness rejection of the instant claims, there is no basis to apply sections 102(f) or 102(g) against the instant claims. Accordingly, there is no basis for the Examiner to require Applicant to state which entity is the prior inventor of any subject matter of the '553 application.

III. Claim Rejections. The rejections set forth in the Office Action are summarized and addressed as follows:

(i) Obviousness-type double patenting. Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 are provisionally rejected over claims 36-96 of co-pending application no. 10/719,553 ("the '553 application"). The '553 application has not issued as a patent. Accordingly, it is requested that the instant rejection be held in abeyance.

(ii) Rejections under 35 U.S.C. §103(a). Claims 1-22, 26, 26, 28, 35, 64 and 66-82 have been rejected as obvious over Ipsen, et al. US 2004/0091500 A1 (Ipsen) and WO 99/47680. Because the respective disclosures of Ipsen and the '680 publication are identical, the rejection is addressed with reference to Ipsen. The same arguments apply equally well to the '680 publication. The Examiner's position is that Ipsen provides motivation to make a recombinant mutant Bet v 1 allergen comprising all of the mutations set forth in Ipsen and that such a mutant would read on the

mutant allergens called for in the instant claims. The rejection is traversed because Ipsen provides no motivation to make the instantly claimed invention.

The Examiner errs in finding a motivation in Ipsen to make a mutant comprising all of the single mutations that are disclosed therein. The obviousness standard requires that the invention be considered as a whole and that there be a motivation to combine elements found in the prior art to arrive at the claimed invention. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005) The mere presence of elements of the claimed invention in the prior art is not sufficient to arrive at the claimed invention, even if it is possible to physically combine the elements. *Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc.*, 183 F.3d 1347, 1356 (Fed. Cir. 1999) ("[N]o basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention.") The motivation to combine prior art teachings "must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Obviousness cannot be predicated on a combination of elements "selectively culled" from the prior art. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998).

In the instant case, there is no motivation to modify Ipsen to arrive at the instantly claimed recombinant allergen with at least four primary mutations, spaced from each other by at least 15Å, wherein the primary mutations are placed in such a manner that at least one circular surface region with an area of 800 Å comprises no mutation. It is improper to combine the individual mutations set forth Ipsen just because it is possible to do so. Nor can the Examiner's asserted motivation that increasing the number of mutations in a mutant allergen reduces IgE binding serve as a proper motivation. Ipsen provides no motivation to choose a recombinant Bet v 1 with all of the disclosed mutations from among any of the other many combinations of Bet v 1 mutations that are possible. Thus, the motivation asserted by the Examiner is general in nature and does not satisfy the requirement for a "clear and particular" motivation to arrive at the claimed recombinant mutant with at least four primary mutations, spaced from each other by at least 15Å, wherein the primary mutations are placed in a manner such that at least one circular surface region with an area of 800 Å comprises no mutation. In the absence of a particular motivation to choose a

Bet v 1 mutant with all of the single mutants in Ipsen, the Examiner has impermissibly "selectively culled" one arrangement of the elements in Ipsen to arrive at the claimed invention.

In choosing a particular combination of elements from among a large possible number of combinations to arrive at the claimed invention, the Examiner has applied an "obvious to try standard." MPEP § 2145, subsection X.B; *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988). "Obvious to try" is not the standard for obviousness. *Id.* In view of the large number of possible mutants that could be formed using the mutations set forth in the Ipsen and the absence of any suggestion of to combine any particular set of mutants to arrive at the instantly claimed invention, the Examiner must have used the teachings of the instant specification modify Ipsen and arrive at the instant claims. Such hindsight is not permitted. *ATD v. Lydall, Inc.,* 159 F.3d 534, 546 (Fed. Cir. 1998). ("Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.")

In final response to the instant rejection, it is noted that the present invention is based on the theory that the claimed recombinant allergens are superior to recombinant allergens in the prior art because the claimed allergens lower IgE binding, and in particular lower the probability of IgE cross-linking, while preserving at least one epitope to generate a B cell response that competes with IgE binding. Thus the instantly claimed allergens lower IgE binding and cross-linking by providing for multiple mutations on the surface of an allergen that are spaced from each other by at least 15 Å. At the same time, the claimed allergens preserve at least one epitope to generate a B cell response by placing the multiple mutations in a manner such that at least one circular surface region with a area of 800 $Å^2$ comprises no mutation. None of the prior art of record suggests that IgE binding should be reduced by making multiple mutations on the surface of an allergen while at the same time preserving an area with no mutation to preserve a B cell epitope. Ipsen, for example, fails to suggest the benefit of making multiple surface mutations while at the same time maintaining a portion of the surface of the allergen with no mutation in order to preserve a B-cell epitope. To

the contrary, Ipsen is based on a destroying a dominant IgE epitope (see Ipsen at paragraph [0047] ("Another important aspect of the rationale behind the current invention is the assertion of the existence of dominant IgE epitopes.") Ipsen, however, suggests no benefit to be derived from making multiple surface mutations that are spaced 15 Å or more apart, while at the same time preserving a B-cell epitope. For this reason additionally, the prior art of record does not suggest the instant claims.

For at least the reasons set forth above, claims 1-22, 35, 64, and 66-82 are not obvious over the prior art of record. Reconsideration of claims 1-22, 35, 64, and 66-82 and withdrawal of the rejections under section 103 is requested.

(iii) Rejections under 35 U.S.C. § 112, first paragraph (written description). Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 are rejected for alleged lack of written description. The rejection is traversed on the grounds that the specification provides sufficient relevant identifying characteristics coupled with sufficient examples to demonstrate that that the inventors were in possession of the claimed invention at the time the application was filed.

The rejected claims are directed to a genus of mutant allergens comprising at least four primary mutations, spaced from each other by at least 15Å, wherein the primary mutations are placed in such a manner that at least one circular surface region with an area of 800 $Å^2$ comprises no mutation. The specification provides adequate written description sufficient to show that the inventors had possession of any such mutant allergen. Hence, the specification beginning at page 27, line 30 provides that the recombinant mutant allergen may be a mutant allergen of an inhalation allergen, pollen allergen, and venom allergens. The specification beginning at page 28, line 19 further sets forth over two dozen protein allergens that are suitable targets for making the claimed recombinant mutant allergen. It is self evident that each of the protein allergens set forth in the specification are composed on the twenty naturally occurring amino acids. Moreover, at the time the invention was filed, many of the protein allergens set forth in the specification had been cloned or purified and sequenced, the three dimensional structure of many of the allergens had been determined, and multiple homologues of many of the allergens had been sequenced, allowing for comparison among family members. See, e.g., King et al., U.S. Patent Publication No.

2003/0039660 A1, Table 8 beginning at page 51, listing references for allergens that have been cloned and/or sequenced, and Table 9 beginning at page 67, listing allergens in the protein database for which the three-dimensional structure was known. It is noted that although King et al. has a filing date of March 3, 2002, the vast majority of the references cited in Tables 8 and 9 therein have publication dates and/or deposit dates that are prior to the earliest claimed priority date of the instant application. Thus, as of the filing date of the present application, on of ordinary skill in the art would immediately recognize that the listing of allergens set forth in the specification referred to the amino acid sequences of allergens that were known and that such amino acid sequences were readily ascertainable.

Moreover, having set forth an extensive listing of naturally occurring allergens for use in the invention, the specification goes on to define the structural characteristics of the claimed recombinant mutant allergens. The specification begins by specifying that amino acids suitable for substitution in accordance with the present invention are surface-exposed amino acids, that such surface-exposed amino acids may be identified on the basis of information of their solvent accessibility, and that in a preferred embodiment the amino acids of an allergen may be ranked according to solvent accessibility and then substituting one or more amino acids among the more solvent accessible ones. Specification at page 34, line 33 through page 35, line 5. The specification further sets out that homology among members of a protein family may be used to identify amino acids for substitution. Specification at page 35, lines 6-34. Further criteria for substitution are set forth on pages 36-38 and in the definitions that appear at pages 41-42. Moreover, the reduction of IgE binding observed for a recombinant mutant allergen of the invention may be determined using any immunoassay known in the art or by assessing reduced IgE binding and the reduced ability of a mutant to initiate Histamine Release (HR), see, e.g., specification at page 26, lines 11-30. Accordingly, the specification sets out a large number of particular naturally occurring allergens that are candidates for making the claimed recombinant mutant allergens, then sets out in detail the structural and identifying features (solvent accessibility, homology) that define which amino acids are to be mutated, sets out that the consequence of such a mutation is lowered IgE binding and further sets out assays that can be used to demonstrate such reduced IgE binding.

The specification further goes on to exemplify the claimed invention with a dozen mutants of the birch allergen, Bet v 1 (see, e.g., specification at page 29, line 19 through page 30, line 31 and page 97, line 35 through page 98, line 34), eleven mutants of the dust mite allergen, Der p1 (specification at page 105, line 10 through page 111, line 25), and 14 mutants of the grass allergen, Phl p 5 (specification at page 111, line 28 through page 120, line 26). Thus, the specification provides 37 specific examples from three completely unrelated allergens that fall within the scope of the claimed invention.

In setting forth the present rejection, the Examiner takes the position that it is "an impossible task" to disclose mutations for all allergens. Compliance with the written description requirement, however, does not require a description of all members of a genus. The written description requirement is met by providing sufficient structural, physical and/or functional properties that describe a genus and/or a sufficient members of genus that show the inventors were in possession of the claimed invention. As set forth above, the specification sets out an extensive written description for the instant claims in the form a description of naturally occurring allergens to be modified, the physical criteria for choosing which amino acids are to be mutated, a description of the functional properties of mutated allergens, and three dozen examples of recombinant allergens within the claimed genus of recombinant mutant allergens. Accordingly, for at least all of the reasons set forth above, the specification provides adequate written description for the full breadth of the instantly claimed invention. Reconsideration of 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 withdrawal of the rejection thereof for lack of written description is requested accordingly.

(iv) Rejection under 35 U.S.C. § 112, first paragraph (enablement). Claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 are rejected for alleged lack of enablement. In response, as set forth above with regard to the written description rejection, at the time the application was filed, the sequence and structure was known for many allergens, the specification provides detailed guidance as to how to make and use the claimed invention, and provides numerous examples of the claimed invention. For at least the reasons set forth above, the specification enables one of ordinary skill in the art to make and use the full scope of the claimed invention without undue experimentation.

In further response to the present rejection, the specific points raised by the Examiner to support and enablement rejection are not well taken. First, the recitation in claim 1 of "substitution of one surface-exposed amino acid residue with another residue" is clear on its face. Thus, the disclosure in the specification that the term "substitution" may mean deletion, substitution or addition of an amino acid does not change the meaning of claim 1, and thus has no bearing on whether claim 1, e.g., is enabled. As discussed in detail above, the specification enables the identification of a particular amino acid to be substituted and then making a substitution, i.e., the replacement of one amino acid with another acid. Second, the specification discloses that sequence alignments may be performed using the program CLUSTAL W. Specification at, e.g., page 44, line 36; page 96, line 45; and page 104, line 15.

In further response to the rejection for lack of enablement, one of ordinary skill in the art would be able to tell whether a mutation is a primary mutation or a secondary mutation. Primary mutation are thus all mutations in a mutant allergen that are at least 15 Å from each other and which are substitutions of surface exposed amino acid residues with other residues that do not occur in the same position in the amino acid sequence of any known homologous protein within the taxonomic species from which said naturally occurring allergen originates. Specification at, e.g., page 19, lines 27-34. See also specification at page 20, lines 14-17 ("primary mutations are defined by their location in respect to each other, i.e., they are spaced apart, to ensure that they are mutations in separate clusters of epitopes.) Any additional mutations that do not meet the requirement as being 15 Å from any other mutation are secondary mutations. Specification at page 25, lines 5-6 (secondary mutations may be located close to a primary mutation).

With respect to claim 22, any at least four mutations that are spaced at least 15 Å from each may be considered primary mutations. Consider, for example, a mutant with four mutations, M1, M2, M3, and M4, each spaced at least 15 Å from each other. Each of M1 - M4 is a primary mutation.. A fifth mutation (M5) added to the mutant allergen may be either a primary or a secondary mutation. If M5 is at least 15 Å from each of M1-M4, M5 is also a primary mutation. The result differs, however, if M5 is, e.g., within 15 Å of M1 and at least 15 Å from each of M2-M4. In such case, either member of the pair of M1 or M5 may be designated a primary mutation.

Upon such designation, the non-designated member of the pair becomes a secondary mutation. The description of the recombinant allergen in terms of the number of primary and secondary mutations, however, does not depend on which of M1 or M5 is designated the primary or secondary mutation. In each case the there will be four primary mutations and one secondary mutation. Similarly, for any set of mutations selected from the point mutants set forth in claim 22, there will be a set number of primary mutations and a set number of secondary mutations. Thus, contrary to the Examiner's position, the skilled artisan can readily make mutants comprising a given number of primary and secondary mutations without undue experimentation.

With final respect to the instant rejection, Applicant notes that the theory of the present invention lies in *retaining* an intact surface area of an allergen, and then, by means of mutations, reducing the IgE reactivity of the remaining surface area (i.e., the remaining epitopes) as much as possible without significantly affecting the overall three-dimensional folding pattern of the mutant. Thus, the amino acid residues that are selected for mutation are chosen on the basis of their location in relation to one another and not on the basis of being located in a dominant IgE binding epitope. It has been found that all surface exposed amino acids are possible targets for substitution and not only the highly conserved ones found in the dominant IgE epitopes. The consequence of this approach is that the risk of prophylactic shock, caused by cross-linking of IgE antibodies and subsequent mast cell activation during a vaccination regimen is significantly reduced by the overall reduced IgE-binding of the surface while retaining immunogenicity of one surface area (epitope). This approach allows for he development of a new immunogenic response that competes more efficiently with the existing IgE response. From the underlying theory it is evident that the present invention may be exploited with any allergen-- there is no requirement for specific mutations that must be common to any group of allergens.

Accordingly, for at least all of the reasons set forth above, the specification enables one of ordinary skill in the art to make and use the invention of claims 1-22, 25, 26, 28, 35, 37-39, 64 and 66-85 without undue experimentation. Reconsideration of the claims and withdrawal of all rejections thereof for lack of enablement is requested.

(v) Rejections under 35 U.S.C. §112, second paragraph. The indefiniteness rejections set forth by the Examiner are addressed as follows:

(a) The rejection of claims 3, 15, 37-39 and 83-85 for alleged indefiniteness based on the assertion that the criteria for placement of primary and secondary mutations makes the claim indefinite has been addressed in the response to the enablement rejection (in which the Examiner raised the same point), *supra*. As discussed in detail above, for a given set of mutations in a recombinant mutant allergen, there will be a fixed number of primary and secondary mutations. In response to the Examiner's specific question, "[W]hat is the minimum number of mutations present in a recited allergen that comprises secondary mutations," the answer is "five." Each claimed allergen must have a minimum of four primary mutations. From the discussion *supra,* it is evident that a mutation in a particular recombinant allergen cannot simultaneously be a primary and secondary mutation. Thus, there must be at least one additional, fifth mutation in order have a secondary mutation.

(b) In response to the Examiner's objection to the term "variant," claim 37 has be re-worded. The scope of claim 37 is unchanged.

(c) In response to the Examiner's request, claim 22 has been amended to use a single nomenclature. The scope of claim 22 is unchanged.

For at least the reasons set forth above, each of claims 3, 15, 22, 37-39 and 83-85 complies with section 112, second paragraph. Reconsideration of the claims and withdrawal of all rejections thereof for alleged indefiniteness is requested.

CONCLUSION

This application is believed to be in condition for allowance, which is earnestly solicited.

If the Examiner believes there are remaining issues the could be addressed by an interview or by entry of an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned attorney at the Examiner's convenience.

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Respectfully submitted,

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